REMARKS

Claims 1-11 and 15-27 are pending in this application.

The outstanding rejections are addressed individually below.

1. ***Claims 1-11 of the present invention are not unpatentable over claim 1 of U.S. Patent No. 5,591,721.***

Claims 1-11 stand rejected under the judicially created doctrine of obviouness-type double patenting as allegedly being unpatentable over claim 1 of U.S. Patent No. 5,591,721. Applicants respectfully traverse this rejection.

Claims 1-11 are not a species of the genus of the method of claim 1 of U.S. Patent No. 5,591,721 because the oligonucleotide used in this method requires "phosphorothioate internucleoside linkages between every nucleoside." In contrast, the claims of the present invention require "at least one phosphorothioate internucleotide linkage and at least one internucleotide linkage selected from the group consisting of alkylphosphonate, phosphorodithioate, alkylphosphonothioate, phosphoramidate, phosphoramidite, phosphate ester, carbamate, carbonate, phosphate triester, acetamidate, and carboxymethyl ester . . . ." (emphasis added) Thus, at least two different internucleotide linkages are required in the present claims as opposed to only one type in the '721 patent.

Applicants respectfully submit that the specification of the '721 patent does not teach that phosphorothioate linkages are alkylphosphonate, phosphorodithioate, alkylphosphonothioate, phosphoramidate, phosphoramidite, phosphate ester, carbamate, carbonate, phosphate triester, acetamidate, or carboxymethyl ester linkages. The specification does recite (at Col. 6, lines 14-19, the section cited by the Examiner) that ". . . non-phosphodiester internucleotide linkages. Such linkages include alkylphosphonates, phosphorothioates, phosphorodithioates, alkylphosphonothioates, alkylphosphonates, phosphoramidates, phosphate esters, carbamates, acetamidate, carboxymethyl esters, carbonates, and phosphate triesters." (emphasis added) Thus, the '721 patent does not disclose that phosphorothioate linkages include these various

types of internucleotide linkages, but rather that non-phosphodiester internucleotide linkages do include these types of internucleotide linkages.

Accordingly, as Applicants submit that the claims of the present invention are patentable over claim 1 of U.S. Patent No. 5,591,721, it is respectfully requested that this rejection be reconsidered and withdrawn.

2. *Claims 1-11 are enabled.*

Claims 1-11 stand rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not enable any person skilled in the art, to use the invention commensurate in scope with these claims. Applicants respectfully traverse this rejection.

Applicants thank the Examiner for the acknowledgment that Applicants' arguments, references that corroborate the teachings of the instant specification, and Declaration under 37 C.F.R. § 1.132 have been found persuasive.

In addition, Applicants note that the statements in the previous Amendment, which are referred to and paraphrased by the Examiner in this Office Action, refer to Applicants invention as claimed in the present application.

Applicants provide the following arguments regarding the Examiner's remaining concerns under 35 U.S.C. § 112, first paragraph.

M.P.E.P § 2164.01 states that 35 U.S.C. § 112, first paragraph, "has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation." (citation omitted). The same section further states that "[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation."

The Office Action states at page 4 that "there is a high level of unpredictability in the administration of oligonucleotides to whole organisms, such as taught by Branch for administration of antisense oligonucleotides" and that Branch also teaches that the

capacity to deliver genes *in vivo* requires trial and error experimentation due to unpredictable factors, including stability of oligonucleotides in the whole organism.

Applicants' maintain that their claims are directed to a method for ***introducing into a mammal an oligonucleotide possessing certain recited structural features, whereby the oligonucleotide is present in intact form in plasma at least six hours following oral administration.*** Applicants previously provided arguments, references that corroborate the teachings of the instant specification, and a Declaration under 37 C.F.R. § 1.132, including *in vivo* data, which the Examiner has found persuasive, showing that after introducing into a mammal an oligonucleotide possessing certain recited structural features, the oligonucleotide is present in intact form in plasma at least six hours following oral administration.

Accordingly, Applicants respectfully submit that the claims of the instant application are enabled.

Applicants direct the Examiner's attention to U.S. Patent No. 5,591,721 (attached hereto as Appendix A), which is the patent issuing from the ancestor application to which the instant application claims priority. Applicants respectfully point out that the issued claim in this patent contains language similar to that present in the instant application. That issued claim of the '721 patent recites:

> A method for introducing an intact oligonucleotide into a mammal, the method comprising the step of orally administering an oligonucleotide . . . whereby the oligonucleotide is **present in intact form in the systemic plasma and in liver tissue of the mammal at least six hours following oral administration**. (emphasis added)

Thus, Applicants submit that the specification of the present application is completely enabling for the present claims, as was the specification of the '721 patent for the issued claim in that case.

The Office Action states at page 5, that claimed oligonucleotides complementary to the disease genes in claims 8-11 are not supported by the teaching in the specification as filed as to specific oligonucleotide sequences which show complementarity to the

claimed genes and that the specification does not teach what sites of the claimed genes as broadly claimed would be available to such complementary application of an oligonucleotide. The Office Action further states that the lack of teaching in the specification as filed as to the specific conditions allowing for complementarity of an oligonucleotide to the broad genus of claimed genes lends a great deal of unpredictability to the design and application of such oligonucleotides and that it would require undue experimentation to make and use the invention as claimed. Applicants respectfully disagree

Applicants respectfully submit that such teachings are not necessary to practice the claimed invention. However, despite the fact that Applicants submit that such teachings are not necessary to practice the claimed invention, as discussed in the Amendment under 37 C.F.R. § 1.111, filed April 3, 2003, the specification does teach that various effective antisense nucleotides have already been described for many different known viral nucleic acid sequences (*see, e.g.*, specification, page 27, lines 3-18). The specification further states that nucleic acid sequences are known or have been described for other viruses and pathogenic organisms, to which antisense sequences could be made (specification, page 27, lines 19-30 and page 28, line 28 to page 29, line 8). Furthermore, Craig, et al. (*Exp. Opin. Ther. Patents* (1997) 7(10):1175-1182; attached as Appendix C to the Amendment under 37 C.F.R. § 1.111, filed April 3, 2003) teaches at page 1177 that once a modification to the oligonucleotide backbone "is found to confer a favorable characteristic, it can then be used in oligonucleotides having *different* sequences of nucleosides and, thus, provide utility for the treatment of other diseases" (emphasis added) as well as discussing information regarding the patentability of antisense technology.

Thus, in view of these arguments and the issued '721 patent, Applicants respectfully submit that claim 1 and claims 2-11 dependent thereon are enabled.

Accordingly, Applicants respectfully request that this rejection under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

3. ***Claims 15-22 of the present invention are not unpatentable over claim 1 of U.S. Patent No. 5,591,721.***

Claims 15-22 stand rejected under the judicially created doctrine of obviouness-type double patenting as allegedly being unpatentable over claim 1 of U.S. Patent No. 5,591,721. Applicants respectfully traverse this rejection.

The oligonucleotides described in the method of claims 15-22 of the present invention are not a species of the genus of the oligonucleotide described in the method of claim 1 of U.S. Patent No. 5,591,721 because the oligonucleotide used in the method of the '721 patent requires "phosphorothioate internucleoside linkages between every nucleoside." In contrast, claims 15-22 of the present invention require "at least one phosphorothioate internucleotide linkage and at least one internucleotide linkage selected from the group consisting of alkylphosphonate, phosphorodithioate, alkylphosphonothioate, phosphoramidate, phosphoramidite, phosphate ester, carbamate, carbonate, phosphate triester, acetamidate, and carboxymethyl ester . . . ." (emphasis added) Thus, at least two different kinds of nucleotide linkages are required, not just phosphorothioate internucleotide linkages.

Furthermore, as discussed above, Applicants respectfully submit that the '721 patent does not disclose that phosphorothioate linkages include these various types of internucleotide linkages, but rather that non-phosphodiester internucleotide linkages do include these types of internucleotide linkages.

Accordingly, as Applicants submit that claims 15-22 of the present invention are patentable over claim 1 of U.S. Patent No. 5,591,721, it is respectfully requested that this rejection be reconsidered and withdrawn.

4. ***Claims 23-27 of the present invention are not unpatentable over claim 1 of U.S. Patent No. 5,591,721.***

Claims 23-27 stand rejected under the judicially created doctrine of obviouness-type double patenting as allegedly being unpatentable over claim 1 of U.S. Patent No. 5,591,721. Applicants respectfully traverse this rejection.

The oligonucleotides described in the method of claims 23-27 of the present invention are not a species of the genus of the oligonucleotide described in the method of claim 1 of U.S. Patent No. 5,591,721 because the oligonucleotide used in the method of the '721 patent requires "phosphorothioate internucleoside linkages between every nucleoside." In contrast, claims 23-27 of the present invention require "at least one phosphorothioate internucleotide linkage" and "at least two alkylphosphonate internucleotide linkages at its 3' and 5' terminal ends . . . ." (emphasis added) Thus, at least two different internucleotide linkages are required at three sites (one phosphorothioate and two alkylphosphonate internucleotide linkages).

Furthermore, as discussed above, Applicants respectfully submit that the '721 patent does not disclose that phosphorothioate linkages include alkylphosphonate internucleotide linkages, but rather that non-phosphodiester internucleotide linkages do include alkylphosphonate internucleotide linkages.

Accordingly, as Applicants submit that claims 23-27 of the present invention are patentable over claim 1 of U.S. Patent No. 5,591,721, it is respectfully requested that this rejection be reconsidered and withdrawn.

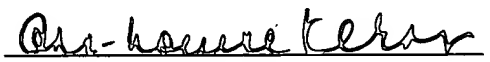
CONCLUSIONS

In view of the arguments set forth above, Applicants respectfully submit that the rejections contained in the Office Action mailed on July 2, 2003, have been overcome, and that the claims are in condition for allowance. If the Examiner believes that any further discussion of this communication would be helpful, she is invited to contact the undersigned at the telephone number provided below.

Applicants enclose herewith a petition for a two month extension of time pursuant to 37 C.F.R. § 1.136, up to and including December 2, 2003, to respond to the Examiner's Office Action mailed on July 2, 2003. Please charge deposit account no. 08-0219 the $210.00 fee for this purpose.

No other fees are believed to be due in connection with this response. However, please charge any underpayments or credit any overpayments to Deposit Account No. 08-0219.

Respectfully submitted,



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Appendix A: U.S. Patent No. 5,591,721